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Acetyl-L-Carnitine in Attention-Deficit/Hyperactivity Disorder: A Multi-Site, Placebo-Controlled Pilot Trial

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Abstract

Objective:

To determine whether acetyl-L-carnitine (ALC), a metabolite necessary for energy metabolism and essential fatty acid anabolism, might help attention-deficit/hyperactivity disorder (ADHD). Trials in Down's syndrome, migraine, and Alzheimer's disease showed benefit for attention. A preliminary trial in ADHD using L-carnitine reported significant benefit.

Method:

A multi-site 16-week pilot study randomized 112 children (83 boys, 29 girls) age 5-12 with systematically diagnosed ADHD to placebo or ALC in weight-based doses from 500 to 1500 mg b.i.d. The 2001 revisions of the Conners' parent and teacher scales (including DSM-IV ADHD symptoms) were administered at baseline, 8, 12, and 16 weeks. Analyses were ANOVA of change from baseline to 16 weeks with treatment, center, and treatment-by-center interaction as independent variables.

Results:

The primary intent-to-treat analysis, of 9 DSM-IV teacher-rated inattentive symptoms, was not significant. However, secondary analyses were interesting. There was significant ($p = 0.02$) moderation by subtype: superiority of ALC over placebo in the inattentive type, with an opposite tendency in combined type. There was also a geographic effect ($p = 0.047$). Side effects were negligible; electrocardiograms, lab work, and physical exam unremarkable.

Conclusion:

ALC appears safe, but with no effect on the overall ADHD population (especially combined type). It deserves further exploration for possible benefit specifically in the inattentive type.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common childhood mental health problem and often persists into adulthood. It is characterized by inattentiveness, distractibility, disorganization, overactivity, and impulsiveness. Although several well-documented treatments are available (FDA-approved medications and behavioral treatment), the search continues for additional treatment options, especially for those who do not respond to established treatment, who have severe side effects, or who have personal preference to avoid schedule II or IV medication. L-carnitine is one of many alternatives considered on theoretical grounds.

L-carnitine is a natural mammalian metabolite necessary for fatty-acid metabolism and energy production (Brass, 1992). It acts as a carrier in the transport of long chain fatty acids across the inner mitochondrial membrane for β-oxidation in all tissues; in skeletal and cardiac muscle, β-oxidation supplies the major fuel (Brass 1992; Bremer 1983). L-carnitine not only binds fatty acids for their mitochondrial oxidation, but also plays a role in removing potentially toxic metabolic intermediates, such as carboxylic acids (Brass 1992,1994; Chalmers et al. 1983; De Sousa et al. 1986; Roe et al. 1984). Carnitine is present in high concentrations in all tissues as either free carnitine or as acylcar-nitines, which include acetyl-L-carnitine (ALC), its most abundant short chain ester (Goa and Brogden 1987).

Omnivorous humans synthesize only 25% of daily carnitine requirement themselves, the other 75% coming from the diet (daily requirements are approximately 200 mg) (Rebouche and Seim 1998). Acetyl-L-carnitine is synthesized from l-carnitine by the enzyme carnitine acyl-transferase (CAT), located on the matrix side of the inner mitochondrial membrane (Bremer 1983). CAT is also able to catalyze the reverse reaction, releasing acetate, a key metabolite in the trafficking between neurons and glia (Sonnewald et al. 1993).

The effect of ALC on brain metabolism and function has been studied in several experimental models. Energy metabolism of the brain has been studied with spectroscopy (^{31}P and ^{1}H nuclear magnetic resonance) in animal models, which has shown that ALC can stimulate lipid-mediated energy production in the central nervous system (CNS) (Gorini et al. 1998; Kuratsune et al. 1997; Maccari et al. 1990; Sonnewald et al. 1993). In addition, the role of acetate moieties released from CAT in lipid metabolism has been studied using radioactive ALC, showing that the acetyl moiety of ALC was incorporated into saturated (60%), monounsaturated (15%), and polyunsaturated (25%) fatty acids. Injection in the ventricle of radioactive glucose, the major source of acetyl-CoA in the CNS, revealed that glucose was a precursor of saturated (85%) and monounsaturated (15%) but not of polyunsaturated fatty acids (Ricciolini et al. 1998).

ALC is suspected of having an impact on several neurotransmitter pathways, particularly cholinergic and downstream dopaminergic. The drug affects mitochondrial respiration by increasing cytochrome oxidase activity and reducing glutamate dehydrogenase activity in rat mitochondria, indicating a possible effect on neurotransmitter metabolism at a synaptic level (Gorini et al. 1999). The cholinergic effects have been tested in rat brain synaptosomal preparations, which confirmed that ALC could provide the acetyl moiety that transfers to choline, generating acetylcholine, thereby acting as a precursor of this neurotransmitter (Dolezal and Tucek 1998). In addition, ALC also exerts mild M_3 muscarinic receptor agonism in rats, simulating acetylcholine release (Imperato et al. 1989). The compound significantly increases glutamatergic receptor binding, and protects against age-related reductions in the GABA/benzodiazepine

receptor binding capacity (White and Scates 1990).

Previous clinical studies indicate that some physical symptoms in ADHD are similar to symptoms observed in essential fatty deficiency (Burgess et al. 2000; Colquhoun and Bounday 1981; Stevens et al. 1995). Arduini et al. (1992, 1994) reported that carnitine is required to incorporate arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-6), into red blood cell membranes. In an established rat model that produces hyperactivity and learning deficit following neonatal anoxia, ALC has improved learning and reduced hyperactivity (Dell'Anna et al 1997). In a small double blind, placebo-controlled trial, ALC (50 mg/kg b.i.d.) significantly reduced hyperactivity in school-aged boys diagnosed with the fragile X syndrome (Torrioli et al. 1999). De Falco (1994) reported benefit on memory and attention in an open study in patients with Down's syndrome. In a placebo-controlled trial in pediatric migraine, Nicolodi and Sicuteri (2000) also reported significantly improved attention and memory with ALC 25 mg/kg. Van Oudheusden reported that L-Car-nitine 100 mg/kg/day exerted a significant beneficial effect on inattention in children with ADHD in a crossover study (Van Oudheusden and Scholte 2002). Thus there are both animal and human data suggesting a role for l-carnitine and its moieties in brain function, fatty acid metabolism, neurotransmission, and attention.

Therefore we undertook a multi-site, placebo-controlled pilot study in well-diagnosed children with ADHD, using pharmaceutical-grade ALC.

Method

In a multi-site parallel-group double-blind randomized pilot trial, children age 5-12 with DSM-IV ADHD diagnosed by Diagnostic Interview Schedule for Children (Shaffer et al. 1996) and by clinical evaluation by a licensed physician or psychologist were randomly assigned to either placebo or acetyl-l-carnitine for 16 weeks, with parent-and teacher-rated scales at baseline, 8 weeks, 12 weeks, and 16 weeks. Written permission from parents and assent from children were obtained using informed consent documents and procedures approved by the local institutional review boards before any study assessments or treatment.

Inclusion criteria

Inclusion criteria were: boys and girls age 5–12 with investigator-diagnosed ADHD (any of the 3 subtypes) confirmed by the Diagnostic Interview Schedule for Children (DISC-IV); an item mean on either the 18 DSM-IV ADHD symptoms or nine inattentive symptoms of 1.5 or more (on a 0 to 3 scale) averaging both informants (parent and teacher); reasonably good health during the four weeks immediately prior to initial screening as demonstrated by medical history, physical examination, and laboratory testing; failure of FDA-approved therapy or stopped therapy due to adverse events or declined or stopped approved therapy because of parental/guardian concern about the risks of approved drugs. (Categorical diagnosis followed DSM-IV criteria based on clinical interview of parent and child, assisted by the DISC-IV. In addition, a dimensional criterion of 1.5 item mean rating of ADHD symptoms (either nine inattentive or all 18) was taken from the DSM-IV items embedded in the Conners' (2001) revised long version parent and teacher scales.)

Exclusion criteria

Exclusion criteria were: severe medical, surgical, or neurological problems; anything that would interfere with treatment or assessment; co-morbid diagnoses requiring treatment with psychoactive medication; a prior history of carnitine therapy in the past three months prior to baseline; use of any investigational drug in the 30 days prior to baseline; use of any medication or

supplement to treat ADHD; a frank deficiency of magnesium or zinc, increased levels of lead above 10mcg/dL; impaired renal or liver function; pathologically abnormal peripheral blood count; neuroleptic medication in the past six months; body weight below 13.5 kg, missing one-quarter of school days in the previous two months; another child in the same household or classroom already in the study; no telephone; a non-English speaking primary caretaker; important changes expected in school or home situation, (divorce, relocating) during the course of the trial period; or actively suicidal or homicidal.

Treatment

Participants were treated with either pharmaceutical-grade ALC or identical-appearing and tasting placebo as a soluble strawberry-flavored powder in doses ranging from 500 mg to 1500 mg b.i.d. depending on the weight of child: 13.5-30 kg = 0.5 g b.i.d.; >30-50 kg = 1.0 g b.i.d.; and >50 kg = 1.5 g b.i.d. If a subject crossed a weight threshold during the trial, the dose was increased to the new weight class; this happened only once.

Measure

Behavior and attention were assessed by Conners' revised long version parent and teacher scales (Conners, 2001) at baseline, 8 weeks, 12 weeks, and 16 weeks. The primary outcome measure was the mean of the 9 DSM-IV inattention symptoms embedded in the Conners' Teacher Rating Scale—Revised (CTRS-R), which rates symptoms and problems from 0 (not at all) to 3 (very much or very often). This was selected as primary because preliminary data from Alzheimer's disease, migraine, and Down's syndrome research and a previous small pilot study in ADHD had suggested more effect on attention than on hyperactivity-impulsivity, and teacher observations were considered the best naturalistic measure of attention. Secondary measures included all 18 DSM-IV symptoms by teacher and parent, the Conners' Scale totals by parent and teacher as global measures, and Clinical Global Impressions (CGI) (Guy 1976) by clinician at baseline, 8, 12, and 16 weeks. The CGI has two scales: Severity (CGI-S) and improvement (CGI-I), both scored 1-7, with lower number better. A CGI-S of 1 is normal, 2 borderline, 3 mild, and 4 moderate. A CGI-I of 1 (very much improved) or 2 (much improved) was considered a favorable response to be considered a "responder." Safety measures included vital signs and recording of adverse events at 8, 12, and 16 weeks, and blood counts/chemistries, urinalysis, and electrocardiograms (ECGs) at baseline and 16 weeks.

Data analysis

Treatment balance for age, sex, race, and subtype of ADHD was tested, and the baseline scores of the primary and secondary outcome measures were tested for treatment-group bias. Continuous variables were tested with a one-way analysis of variance (ANOVA). Categorical variables were tested with a general chi-square test (or Fisher's exact test if any expected cell count was < 5). The primary intention-to-treat (ITT) analysis on the change from baseline to week 16 in teacher-rated 9 inattentive symptoms was an ANOVA model that considered the treatment, the center, and the treatment-by-center interaction as the independent variables. Alpha was set at 0.05 for the single primary outcome test. The same analysis was repeated for the secondary outcomes of change in parent and teacher-rated 18 DSM-IV ADHD symptoms and total Conners' sums, with alpha set at 0.05 because of the exploratory nature of the additional tests. CGI scores were summarized descriptively without statistical test: a score of 1 or 2 on the CGI-I counted as a response, and at the other end of the scale, scores of 5-7 were counted as worse. Exploratory moderator analyses for sex, age, ADHD subtype, and weight were performed by adding them to

the intention to treat (ITT) analysis of the primary outcome and deriving the interaction term. Similarly, a mediator analysis of dose was performed. Safety variables were compared by treatment group.

Results

One hundred eighteen children were randomized (60 placebo and 58 ALC) and started treatment; 112 had at least one post-baseline assessment available for intent-to-treat analysis; 92 completed 8-week assessment, and 81 completed the whole study. Of 58 children randomized to ALC, 42 completed, for an attrition rate of 28%. For placebo, 39 out of 60 completed, for an attrition rate of 35%. The treatment-group difference was accounted for by attrition of combined type, greater in placebo (13/33, 39%) than in ALC (9/38, 24%) Attrition of inattentive type for placebo (7/25) was comparable to that of ALC (6/18). By study end, the placebo group was almost evenly balanced between inattentive and combined type (18 and 20, respectively) while the ALC group had more than twice as many combined (29) as inattentive (11) type. Sample characteristics of ITT population (n = 112) are shown in Table 1.

Outcome data are shown in Table 2. There was no significant difference on the main ITT outcome, teacher-rated inattention. ITT analyses of secondary measures also failed to find a significant difference. However, exploratory moderator analyses showed a couple of provocative findings.

	Count (%) or Mean ± SD	
	Placebo (n = 59)	*ALC* (n = 53)
Age, years	8.3 ± 2.2	8.4 ± 2.3
Male	42 (71%)	41 (77%)
Caucasian	41 (70%)	36 (68%)
ADHD, Inattentive Type	25 (42%)	15 (28%)
Combined Type	32 (54%)	35 (66%)
Hyperactive/Impulsive Type	2 (3%)	3 (6%)
Oppositional-defiant disorder	7 (12%)	5 (9%)
Other comorbidity	8 (14%)	11 (21%)
Previous ADHD medication	23 (39%)	16 (30%)
Daily RDI multivitamins	9 (15%)	2 (4%)
CGI-Severity (1-7 scale; 1 = normal, 4 = moderate, 5 = marked)	4.4	4.6
Retention to end of DB of the 118 randomized	39/60 (65%)	42/58 (72%)
Weight-based dose assignment		
0.5 g b.i.d.	30 (50%)	28 (48.3%)
1.0 g b.i.d.	23 (38%)	23 (39.7%)
1.5 g b.i.d.	7 (11.7%)	7 (12.1%)

*ITT = those with at least one post-treatment assessment; N = 112; DB = double blind.

Table 1. Sample Characteristics of Intention-to-Treat Sample (ITT)*

The primary outcome measure (ADHD inattentive symptoms) showed a significant (p = 0.02) moderating effect of diagnostic subtype in the ITT sample due to the inattentive type of ADHD showing superiority of ALC over placebo, in contrast to the combined type showing a tendency the opposite direction. The interaction (Fig. 1) was significant (p = 0.02) even

		n = 112		
		Placebo (n = 59) Mean ± SD	ALC (n = 53) Mean ± SD	p
9-Item Inattention symptom rating by teacher	Baseline	2.23 ± 0.54	2.15 ± 0.59	0.447
	End (wk 16)	1.91 ± 0.72	1.93 ± 0.74	
18-Item ADHD symptom rating by teacher	Baseline	1.87 ± 0.58	1.85 ± 0.61	0.235
	End	1.62 ± 0.71	1.72 ± 0.74	
9-Item Inattention symptom rating by parent	Baseline	2.26 ± 0.47	2.45 ± 0.47	0.289
	End	1.94 ± 0.71	2.02 ± 0.73	
18-Item ADHD symptom rating by parent	Baseline	2.04 ± 0.47	2.22 ± 0.49	0.318
	End	1.77 ± 0.66	1.84 ± 0.68	
Full Conners'-Revised rating by teacher	Baseline	1.40 ± 0.45	1.40 ± 0.52	0.448
	End	1.25 ± 0.57	1.31 ± 0.58	
Full Conners'-Revised rating by parent	Baseline	1.45 ± 0.39	1.58 ± 0.39	0.291
	End	1.25 ± 0.45	1.28 ± 0.49	
CGI-I	Week 8	4 (7%)	7 (13%)	N.S.
N(%) 1 or 2 (responder)	End (wk 16)	8 (14%)	9 (17%)	
CGI-I	Week 8	2 (3%)	1 (2%)	N.S.
N(%) 5–7 (worse)	End (wk 16)	7 (12%)	2 (4%)	

*Primary outcome measure regardless of subtype.

As planned from study inception, the 9 hyperactive-impulsive symptoms were not separately analyzed, but were included in the 18 DSM-IV-TR symptoms.

CGI-I = Clinical Global Impressions-Improvement.

Table 2. ADHD symptom outcome, rated by teachers and parents on conners' rating scales—revised (Intention-to-Treat Population). All Scores Except CGI-I are Item Means on 0–3 Metric

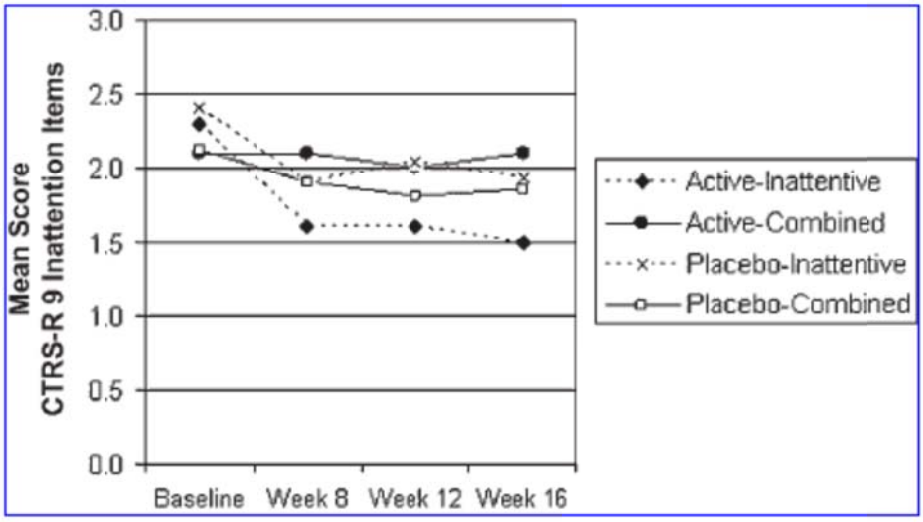

Fig. 1. Interaction of attention-deficit/hyperactivity disorder (ADHD) Subtype with Treatment Condition in the intention-to-treat (ITT) Population. P=0.02 after controlling for sex. CTRS = item mean of 9 inattentive ADHD symptoms on Conners' Teacher Rating Scale-Revised (CTRS-R), the primary outcome variable for the whole trial. Lower score is better.

after controlling for sex, which is well known to be confounded with subtype.

There was also an interesting geographic effect (Fig. 2): When the three sites located about 100-150 miles northwest of the Allegheny Mountains (n = 44) were compared to all the other sites (n = 68) on the ITT primary outcome, the interaction of site and treatment was significant (p = 0.047) due to the three NW-of-Alleghenies sites showing superiority of ALC and the other sites showing a tendency the opposite direction. This effect could not be explained by those three sites having a higher proportion of inattentive type (41% vs. 31%) because subtype was covaried in the analysis. Moderator/mediator analyses by sex, age, weight, and dose were not significant.

There were no safety problems (Table 3). Vital signs and adverse events were not significantly different between treatment groups, and electrocardiograms and physical exams were unremarkable.

Fig. 2. Site distribution. Three sites with solid circles are 100-150 miles northwest of Allegheny Mountains;